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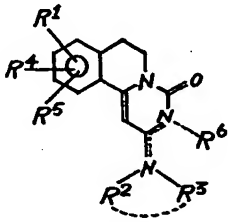
(54) PYRIMIDO(6,1-a)ISOQUINOLIN-4-ONE DERIVATIVES

(71) We, HOECHST AKTIENGESELLSCHAFT a body corporate organised according to the laws of the Federal Republic of Germany, of 6230 Frankfurt/Main 80, Postfach 80 03 20, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pyrimidine derivatives, to intermediates used in their preparation and to processes for the preparation of the intermediates and the compounds of the invention.

The present invention provides pyrimido(6,1-a) isoquinolin-4-one derivatives of the general formula I

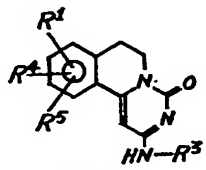


(I)

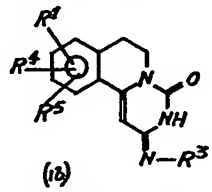
in which R^1, R^4 and R^5, which may be the same or different, each stands for a hydrogen atom, a hydroxy, alkoxy, dialkylphosphinylalkoxy, or acyloxy group, or a halogen atom, and two of the radicals R^1, R^4 and R^5 when in adjacent positions together may form a methylenedioxy or an ethylenedioxy group; R^2 and R^3, which may be the same or different, each stands for a hydrogen atom, a hydroxy, alkoxy, amino, alkylamino, dialkylamino, or arylamino group, or an amino or alkyl group substituted by a 5- or 6-membered carbon ring containing up to 3 hetero atoms, which may be the same or different, selected from nitrogen, oxygen and sulphur atoms, or an alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, halogenoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aralkyl, dialkylphosphinylalkyl, acyl or optionally substituted aryl group, aryl denoting an aromatic hydrocarbon radical having up to 10 carbon atoms, a heterocyclic radical, preferably as defined above; or R^2 represents a pair of electrons if R^3 stands for one of the radicals defined below, or R^2 and R^3 when taken together with the nitrogen atom to which they are bound may form an optionally substituted nitrogen

containing heterocycle which may contain a further nitrogen or oxygen atom; and R^6 stands for a hydrogen atom or an alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, halogenoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aralkyl, heterocyclically substituted alkyl, dialkylphosphinylalkyl, acyl or optionally substituted aryl group, or R^6 represents a pair of electrons if R^2 represents one of the radicals defined above; and the acid addition salts and quaternary ammonium salts thereof.

In the case when at least one of the two radicals R^2 and R^3 represents a hydrogen atom, the above definition of the pyrimido(6,1-2)isoquinolin-4-one derivatives also encompasses the isomers of the following formula Ib, which may be obtained, by complete isomerization of the corresponding compound of formula Ia or which is in equilibrium with the corresponding compound of formula Ia.

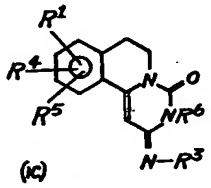


(Ia)



(Ib)

The definition of the pyrimido(6,1-a)isoquinolin-4-one derivatives of the invention also encompasses the isomer of formula Ic



(Ic)

in which R^1, R^2, R^3, R^4, R^5 and R^6 have the above meanings.

If R^1, R^2, R^3, R^4 and R^5 stand for alkoxy groups those having up to 3 carbon atoms are preferred.

Preferred acyloxy radicals R^1, R^4 and/or R^5 are those in which the acyl group is a linear or branched C_1—C_6 alkanoyl group, for example an acetyl group, or an aroyl group, especially a benzoyl group, in which the phenyl nucleus may be substituted one to three times by the same or different substituents selected from halogen atoms, nitro, hydroxy, C_1—C_3 alkoxy and C_1—C_3 alkyl groups.

If R^1, R^4 and/or R^5 stands for a halogen atom, chlorine is preferred.

A dialkylphosphinylalkoxy radical R^1, R^4 and/or R^5 is preferably one in which the alkyl and alkoxy moieties each contains at most 6, advantageously up to 3 carbon atoms, for example dimethylphosphinylmethoxy.

Preferred alkylamino and dialkylamino radicals for R^2 and/or R^3 are those in which the alkyl groups have at most 3 carbon atoms, for example, methylamino or dimethylamino.

Preferred arylamino radicals R^2 and/or R^3 are phenylamino radicals in which the phenyl residue may be substituted one or several times by the same or different substituents selected from halogen atoms, for example, chlorine, C_1—C_3 alkyl groups, for example methyl, and nitro groups. A suitable nitrogen-containing heterocyclic-amino radical for R^2 or R^3 is, for example, an N-morpholinoamino radical.

An alkyl radical R^2, R^3 and/or R^6 is especially one having at most 6 carbon atoms, for example a methyl, ethyl, *n*-propyl, isopropyl, butyl, isobutyl, sec.butyl or tert.butyl radical.

A cycloalkyl radical R^2, R^3 and/or R^6 is preferably one having at most 6 carbon atoms, for example, cyclohexyl.

If R^2, R^3 and/or R^6 represents a substituted alkyl radical this is, for example, an alkyl group having up to 6 carbon atoms and substituted by one or two hydroxy or C_1—C_3 alkoxy groups, halogen atoms, for example chlorine, amino or di(C_1—C_4 alkyl)amino groups, or dialkylphosphinylalkyl groups, for example dimethylphosphinylmethyl.

Examples of aralkyl radicals R^2, R^3 and/or R^6 are those having at most 8 carbon atoms, in which the aryl radical may be mono- or polysubstituted, especially substituted one, two, or three times by the substituents defined above for R^1.

Heterocyclic-alkyl radicals R^2, R^3 and/or R^6 are, for example, furfuryl and tetrahydrofurfuryl radicals.

Examples of aryl radicals R^2, R^3 and/or R^6 are phenyl radicals optionally substituted one or several times, preferably one, two or three times, by the same or different substituents selected from halogen atoms, for example fluorine, chlorine and bromine atoms, C_1—C_3 alkyl and C_1—C_3 alkoxy groups, for example methyl, ethyl, methoxy and ethoxy groups, halogenoalkyl groups, for example, trifluoromethyl groups, amino and hydroxy groups, in the latter the hydrogen atom optionally being replaced by an alkali metal atom, for example, a sodium atom.

A nitrogen-containing heterocyclic radical is, for example, a pyrrolidino, piperidino, morpholino, or piperazino radical, which may be substituted by one or more substituents selected from alkyl, alkoxy-carbonyl, aryl, and nitrogen containing heterocyclic radicals, the terms alkyl, alkoxy, aryl and nitrogen-containing heterocycle preferably having the above preferred meanings.

Examples of acyl radicals for R^2, R^3 and/or R^6 are linear and branched C_1—C_8 alkanoyl radicals, for example, acetyl radicals, and aroyl for example, benzoyl radicals, wherein the phenyl residue may be substituted one or several times by the substituents defined above for R^2, R^3 and/or R^6 when they represent an aryl radical.

As salts of the pyrimido(6,1-a)isoquinolin-4-one derivatives of the invention there are mentioned by way of example those of inorganic or organic acids, for example, the hydrochlorides, hydrobromides, sulphates, phosphates, acetates, oxalates, tartrates, citrates, maleates, and fumarates.

Suitable quaternary ammonium salts of the pyrimido(6,1-a)isoquinolin-4-one derivatives of the invention are, for example, the salts derived from alkyl halides, for example, methiodides.

Preferred meanings for R^1 to R^6 are: alkoxy for R^1 and R^4, hydrogen for R^5, C_1—C_8 alkyl or phenyl optionally substituted one to three times as defined above for R^2, hydrogen, C_1—C_8 alkyl, cycloalkyl, substituted alkyl, aralkyl, heterocyclic alkyl, substituted aryl and C_1—C_8 alkanoyl for R^3 and R^6.

Particularly preferred compounds of the invention are:

9,10 - dimethoxy - 2 - *tert* - butylamino - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one hydrochloride,

9,10 - dimethoxy - 2 - *sec* - butylamino - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one hydrochloride,

9,10 - dimethoxy - 2 - (2,6 - dimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one,

9,10 - dimethoxy - 2 - (2,4 - dimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one,

9,10 - dimethoxy - 2 - (2 - chloroanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one hydrochloride monohydrate,

9,10 - dimethoxy - 2 - (2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one hydrochloride dihydrate,

9,10 - dimethoxy - 3 - methyl - 2 - mesitylimino - 2,3,6,7 - tetrahydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one hydrochloride,

9,10 - dimethoxy - 3 - acetyl - 2 - mesitylimino - 2,3,6,7 - tetrahydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one,

9,10 - dimethoxy - 2 - (N - methyl - 2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one hydrochloride,

9,10 - dimethoxy - 2 - (N - isopropyl - 2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one,

9,10 - dimethoxy - 3 - isopropyl - 2 - mesitylimino - 2,3,6,7 - tetrahydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one,

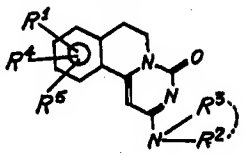
9,10 - dimethoxy - 2 - (N - ethyl - 2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one,

9,10 - dimethoxy - 3 - ethyl - 2 - mesitylimino - 3,4,6,7 - tetrahydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one,

9,10 - dimethoxy - 2 - (N - acetyl - 2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one.

In the following Table I there are listed some of the pyrimido(6,1-a)isoquinolin-4-one derivatives of the invention.

TABLE I



R^5	R^1+R^4	R^2	R^3	melting point of the free base (°C)	Salt	melting point of salt (°C)
H	$9,10(OCH_3)_2$	H	H	—	HCl	300
H	$9,10(OCH_3)_2$	H	OH	—	HCl	264—266
H	$9,10(OCH_3)_2$	H	NH_2	—	HCl	236—238
H	$9,10(OCH_3)_2$	H		—	HCl . $\frac{1}{2}H_2O$	251
11—OCH_3	$9,10(OCH_3)_2$	H		239—241	—	—
H	$9,10(OCH_3)_2$	H	CH_3	—	2HCl . H_2O	179—181 (decomp.)
H	$9,10(OCH_3)_2$	H	$CH_2CH_2CH_3$	—	HCl	204—207
H	$9,10(OCH_3)_2$	H	$CH_2CH_2CH_3$	173—175	—	—
H	2H	H	$CH_2CH_2CH_2CH_3$	—	HCl	235—237
H	$9,10(OCH_3)_2$	H	$CH_2CH_2CH_2CH_3$	184—190	—	—
H	$9,10(OCH_3)_2$	CH_3	CH_3	—	HCl	180—181
H	$9,10(OCH_3)_2$	CH_2CH_3	CH_2CH_3	219—220	—	—
H	$9,10(OCH_3)_2$	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	67—69	—	—
H	$9,10(OH)_2$	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	293—295	—	—
H	$9,10(OCH_3)_2$	H	$CH(CH_3)_2$	—	HCl	230—233
H	$9,10(OCH_3)_2$	H	$CH_2CH(CH_3)_2$	157—160	—	—
H	$9,10(OCH_3)_2$	H	CH_3 | $CHCH_2CH_3$	—	HCl . H_2O	218—225 (decomp.)
H	2H	H	CH_3 | $CHCH_2CH_3$	—	HCl	133—135
H	$9,10(OH)_2$	H	CH_3 | $CHCH_2CH_3$	—	HCl	290—300

TABLE I (cont.)

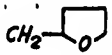
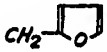
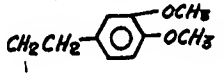
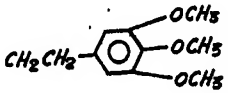
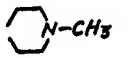
R^5	R^1+R^4	R^2	R^3	melting point of the free base (°C)	Salt	melting point of salt (°C)
			CH_3 |		
11—OCH_3	9,10(OCH_3)$_2$	H	$CHCH_2CH_3$	—	HCl	193—195
H	9,10(OH)$_2$	H	$CH_2CH(CH_3)_2$	305—315 (decomp.)	—	—
H	9,10(OCH_3)$_2$	H	$C(CH_3)_3$	—	HCl	265—270
11—OCH_3	9,10(OCH_3)$_2$	H	$C(CH_3)_3$	—	HCl	222—224
H	2H	H	$C(CH_3)_3$	—	HCl	205—206
H	9,10(OCH_3)$_2$	H	$CH_2CH_2N(C_2H_5)_2$	—	2HCl . H_2O	147—150
H	9,10(OCH_3)$_2$	H	CH_2CH_2Cl	—	HCl	246—248 (decomp.)
H	9,10(OCH_3)$_2$	H	CH_2CH_2OH	203—204	—	—
H	2H	H	CH_2CH_2OH	—	HCl	230—231
H	2H	H	$CH_2CH_2CH(OMe)_2$	154—155	—	—
H	9,10(OCH_3)$_2$	CH_3		166—167	—	—
H	9,10(OCH_3)$_2$	H		237—239	—	—
H	9,10(OCH_3)$_2$	H		—	HCl	199—201
H	9,10(OCH_3)$_2$	H		217—218	—	—
H	9,10(OCH_3)$_2$	H		179—180	—	—
H	9,10(OCH_3)$_2$	H		178—180	—	—
H	9,10(OCH_3)$_2$			—	HCl	233—236
H	9,10(OCH_3)$_2$			—	HCl	233—237
H	9,10(OCH_3)$_2$			183—184	—	—
H	9,10(OCH_3)$_2$			—	HCl	260—263

TABLE I (cont.)

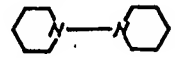
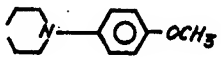
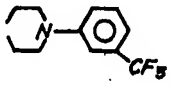
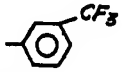
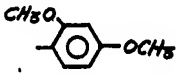
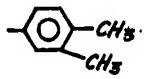
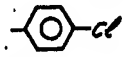
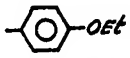
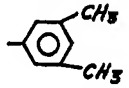
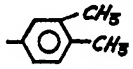
R^5	R^1+R^4	R^2	R^3	melting point of the free base (°C)	Salt	melting point of salt (°C)
H	9,10(OCH_3)$_2$			—	2HCl	215—218
H	9,10(OCH_3)$_2$			—	HCl	153—155
H	9,10(OCH_3)$_2$			220	—	—
H	9,10(OCH_3)$_2$	H		303—305	—	—
H	9,10(OCH_3)$_2$	H		301—302	—	—
H	9,10(OCH_3)$_2$			268—269	—	—
H	9,10(OCH_3)$_2$	H		303—305	—	—
H	9,10(OCH_3)$_2$	H		294—295	—	—
H	9,10(OCH_3)$_2$	H		297—299	—	—
H	9,10(OCH_3)$_2$	H		272—274	—	—
H	9,10(OCH_3)$_2$	H		285—287	—	—
H	2H	H		278—279	—	—

TABLE I (cont.)

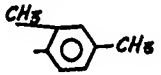
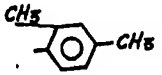
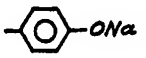
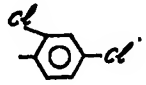
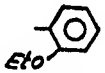
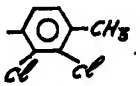
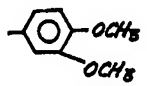
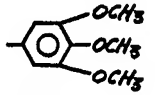
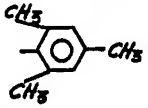
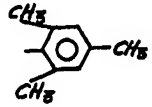
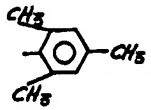
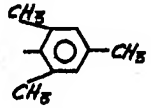
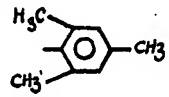
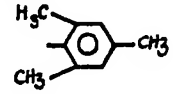
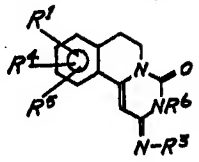
R^5	R^1+R^4	R^2	R^3	melting point of the free base (°C)	Salt	melting point of salt (°C)
H	9,10(OCH_3)$_2$	H		239—241	—	—
11—OCH_3	9,10(OCH_3)$_2$	H		222—225	—	—
H	9,10(OCH_3)$_2$	H		300	—	—
H	9,10(OCH_3)$_2$	H		274—276	—	—
H	9,10(OCH_3)$_2$	H		—	HCl	185—187
H	9,10(OCH_3)$_2$	H		250—251	—	—
H	9,10—O(CH_2)$_2$O	H		235—238	—	—
H	9,10—O(CH_2)$_2$O	CH_2CH_2OH		184—186	—	—
H	9,10(OCH_3)$_2$	H		—	HCl . H_2O	182—186
H	9,10(OCH_3)$_2$	H		—	2HCl	199—203
H	9,10(OPr)$_2$	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	73—75	—	—
H	9,10(OCH_2O)	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	228—230	—	—
H	9,10($OCOCH_3$)$_2$	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	101—103	—	—

TABLE I (cont.)

R^5	R^1+R^4	R^2	R^3	melting point of the free base (°C)	Salt	melting point of salt (°C)
H	9,10(OCH_3)$_2$	H		228—230	—	—
H	9,10(OH)$_2$	H		—	HCl	293—295
H	9,10(OCH_3)$_2$	H		—	HCl . H_2O	238—241
H	9,10(OCH_3)$_2$	H		—	HCl . H_2O	295—297
H	9,10(OCH_3)$_2$	H		—	HCl . $2H_2O$	167—169
H	9,10(OCH_3)$_2$	—$CH(CH_3)_2$		182—183	—	—
H	9,10(OCH_3)$_2$	CH_3		—	HCl	189—191 (decomp.)
H	9,10(OCH_3)$_2$	—$(CH_2)_3$—CH_3		177—178°	—	—
H	9,10(OCH_3)$_2$	—CH_2—CH_3		164—165°	—	—
H	9,10(OCH_3)$_2$	—$COCH_3$		—	—	—

In the following table Ia are listed pyrimido(6,1-a)isoquinolin-2-one derivatives according to the invention the structure of which corresponds to that of isomer Ic. The melting points of the free bases or of the salts are likewise indicated.

TABLE Ia



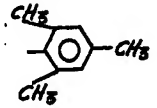
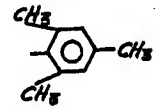
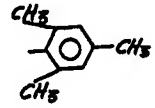
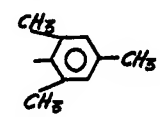
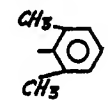
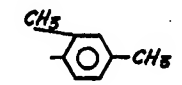
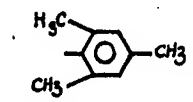
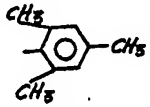
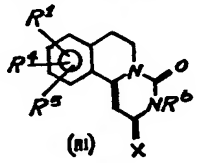
R^5	R^1+R^4	R^6	R^3	melting point of the free bases (°C)	Salt	melting point of salt (°C)
H	9,10(OCH_3)$_2$	—CH_3		151—152	HCl CH_3I	198—200 221—222
H	9,10(OCH_3)$_2$	—$CH(CH_3)_2$		178—179	—	—
H	9,10(OCH_3)$_2$	—$CH_2P(CH_3)_2$ (O)		—	HCl	208—211
H	9,10(OCH_3)$_2$	—CCH_3 (O)		210—212	—	—
H	9,10(OCH_3)$_2$	—CH_3		—	HCl	202—203
H	9,10(OCH_3)$_2$	—CH_3		—	HCl	203—206 (decomp.)
H	9,10(OCH_3)$_2$	—CH_2—CH_3		142—143°	—	—

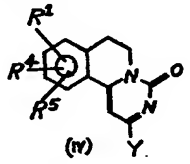
TABLE Ia (cont.)

R^8	R^1+R^4	R^6	R^3	melting point of the free bases (°C)	Salt	melting point of salt (°C)
H	9,10(OCH_3)$_2$	$-CH_2-CH(CH_3)-CH_2NMe_2$		145—146	—	—
H	9,10(OCH_3)$_2$	CH_3	—n—$(CH_2)_3$—CH_3	120—121	—	—

The present invention also provides novel intermediates and their salts suitable for the preparation of the pyrimido(6,1-a)isoquinolin-2-one derivatives of the invention. The intermediates have the formulae III and IV



(III)



(IV)

in which

R^1, R^4, R^5 and R^6 have the above meanings,

X represents an oxygen or sulphur atom and

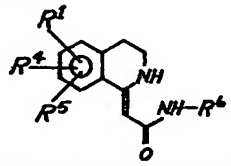
Y represents a halogen atom, for example chlorine, or an alkoxy or alkylthio group, alkoxy and alkyl having the meanings given earlier in this text, with the exception of the compound of formula III in which R^1, R^6, R^4 and R^5 are all hydrogen atoms and X is an oxygen atom (cf. L. Capuano and K. Mueller, Chem. Ber. *108*, 1541 (1975)).

Intermediates of formulae III and IV are listed in Table II, which also includes the melting points of these compounds.

TABLE II

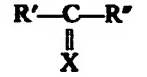
R^1+R^4	R^5	R^6	X	Y	melting point (°C)
2H	H	H	O	—	260°C
2H	H	H	S	—	—
2H	H	—	—	Cl	179—180°
9,10(OCH_3)$_2$	H	H	O	—	323—325°
9,10(OCH_3)$_2$	H	H	S	—	236—237°
9,10(OCH_3)$_2$	H	—	—	SCH_3	203—205°
9,10(OCH_3)$_2$	H	—	—	Cl	235—236°
9,10(OCH_3)$_2$	H	—	—	OBu	158—159°
9,10(OH)$_2$	H	H	O	—	>260°
9,10(OCH_3)$_2$	11—OCH_3	H	O	—	215—218°
9,10(OCH_3)$_2$	11—OCH_3	—	—	Cl	176—178°
H, 10—Cl	H	H	O	—	>250°
H, 10—Cl	H	—	—	Cl	>250°
9,10(OCH_3)$_2$	H	CH_3	O	—	260—262°
9,10(OCH_3)$_2$	H	CH_3	S	—	230—231°
9,10(OCH_3)$_2$	H	$CH(CH_3)_2$	O	—	190—192°

The present invention further provides a process for the preparation of the intermediates of formula III in which X is an oxygen atom, which comprises reacting a compound of formula V



V

in which R^1, R^4, R^5 and R^6 have the aforesaid meanings with a compound of the formula



in which X represents an oxygen atom, R′ and R″, which may be the same or different, each represents a halogen atom or an amino or alkoxy group, or R′ is alkoxy and R″ is a halogen atom.

This reaction may be carried out according to known methods (cf. Shaw & Wooley, J. Biol. Chem. *181*, 89 (1949); A. Dornow & D. Wille, Chem. Ber. *98*; 1505 (1965)). As an alkyl halogenoformate, ethyl chloroformate and as a dialkyl carbonate, diethyl carbonate may be used. The preferred base for the reaction is an alkali metal alkoxide, for example, sodium methylate, sodium ethylate, potassium

methylate, or potassium ethylate, an alkali metal hydride, for example sodium hydride, or an organic base, for example an alkyl amine, for example, triethylamine. The reaction may be carried out in a non-polar or a polar solvent, for example, an aromatic hydrocarbon for example, benzene, toluene, or xylene, an alkanol having from 1 to 6 carbon atoms, for example, methanol or ethanol, an ether, for example dioxane or tetrahydrofuran, or another solvent, for example, dimethylsulphoxide, dimethylformamide or hexamethylphosphortriamide. The reaction can be accelerated or completed by the application of heat, for example, by heating to the boiling point of the solvent.

The present invention also provides a process for the preparation of an intermediate of formula III in which X is an oxygen atom and R^6 has the above meaning, which comprises alkylating or acylating a compound of formula III in which X is an oxygen atom and R^6 stands for a hydrogen atom.

The present invention additionally provides a process for preparing an intermediate of formula III in which X is a sulphur atom, which comprises converting a compound of formula III in which X is an oxygen atom to the desired compound, for example, by treatment with an inorganic sulphide.

The present invention further provides a process for the preparation of an intermediate of formula III in which X is a sulphur atom and R^6 stands for an acyl group, which comprises acylating a compound of formula III in which X is a sulphur atom and R^6 stands for a hydrogen atom.

The present invention provides a process for preparing an intermediate of formula IV in which Y is a halogen atom, which comprises converting a compound of formula III in which X is an oxygen atom into the desired compound, for example, with an inorganic halide.

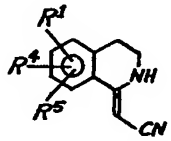
The present invention further provides a process for preparing an intermediate of formula IV in which Y is an alkoxy group, preferably, having at most 6 carbon atoms, which comprises alkoxylating a compound of formula IV in which Y stands for a halogen atom, preferably chlorine, for example, by treatment with an alkali metal alcoholate.

An intermediate of formula IV in which Y is an alkoxy group, preferably having at most 6 carbon atoms, may also be prepared by a different process according to which a compound of formula III in which X is an oxygen atom is reacted with a trialkyloxonium fluoroborate, for example triethyloxonium fluoroborate. The reaction may be carried out in the presence of a solvent, for example a halogenated aliphatic hydrocarbon, for example dichloromethane.

An intermediate of formula IV in which Y is an alkylthio group may be prepared by alkylating a compound of formula III in which X is a sulphur atom, for example, with an alkyl halide, for example methyl iodide.

The compounds of formula V may be prepared by known methods (cf. C.A. *64*, 6627, (1966); Hoffmann La Roche & Co. AG., Netherlands Patent Specification No. 6,401,827, 27th August, 1965).

A starting compound of formula V in which R^6 is a hydrogen atom may also be prepared by the following process, which comprises treating a compound of formula VI

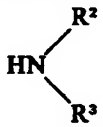


(VI)

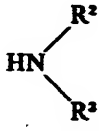
in which R^1, R^4 and R^5 have the above meanings, with the appropriate acid, for example, formic acid, trifluoroacetic acid or polyphosphoric acid. The reaction can be accelerated or completed by heating, for example, to 80 to 150°C.

The compounds of formula VI can be prepared by known methods (cf. C.A. *64*, 6627 (1966), Hoffmann La Roche & Co. AG., Netherlands Patent Specification No. 6,401,827, 27th August, 1965; K. Harsanyi, K. Takaes, E. Bendeh & A. Neszmelyi, Liebigs Ann. Chem. 1606 (1973).

The present invention provides a process for preparing a pyrimido(6,1-a)isoquinolin-4-one derivative of formula I and salts thereof, which comprises reacting a compound of formula III or IV in which R^1, R^4, R^5 and R^6 have the meanings given for formula I and X and Y are as defined for formulae III and IV, with a compound of the formula



in which R^2 and R^3 have the aforesaid meaning, with the proviso, however, that they do not represent acyl groups, preferably in the presence of a base and, if desired, acylating the resulting compound. The compound of the formula



itself can be used as the base, in which case it is added in excess of that required for the reaction, or the base may be an alkali metal hydride, for example sodium hydride, a tertiary amine, for example triethyl amine, or an acid acceptor, for example diazobicyclononene. The reaction may be carried out in the presence of a polar solvent for example, dimethylformamide, dimethyl sulphoxide, a halogenated aliphatic hydrocarbon, for example chloroform, or an alkanol, for example butanol, or in the presence of an aprotic solvent, for example, a high boiling ether, for example, diethylene glycol dimethyl ether. The reaction may be accelerated or completed by the application of heat, for example, by heating to the boiling point of any solvent used.

A further, optional step is the conversion of a resulting free base into a salt or a result salt into the free base.

A compound of formula I in which either R^2 or R^6 represents an alkyl, cycloalkyl, substituted alkyl, aryl, aralkyl, or heterocyclic alkyl group as defined above can be prepared from a compound of formula I in which either R^2 or R^6 is a hydrogen atom by treatment in the presence of a base or of a salt, with a halide of the formula R^2X or R^6X in which R^2 and R^6 are as defined above, and X is a halogen, for example, chlorine bromine or iodine. If R^2 or R^6 represents a phenyl radical, the phenyl nucleus should carry appropriate substituents in order that the halide has a sufficient reactivity. The preferred bases are alkail metal carbonates, for example potassium carbonate, alkali metal hydrides, for example sodium hydride, tertiary amines, such as triethylamine, and acid scavengers, for example, diazobicyclononene. The preferred salts are metal fluorides, for example potassium fluoride. The reaction may be carried out in the presence of a polar solvent, for example dimethylformamide or dimethyl sulphoxide, a halogenated aliphatic hydrocarbon, for example, chloroform, or a ketone for example, acetone, or in the presence of an aprotic solvent, for example a high boiling point ether, for example, diethylene glycol dimethyl ether. The reaction can be accelerated or completed by the application of heat, for example by heating to the boiling point of the solvent. This process is especially suitable for transforming a compound of formula I, in which either R^2 or R^6 denotes a hydrogen atom and R^3 an aryl radical, into the corresponding compound of formula I in which either R^2 or R^6 denotes an alkyl or substituted alkyl group and R^3 stands for an aryl radical.

The process described in the preceding paragraph may lead to quaternary ammonium salts of the isomers of formula I. Alternatively, a resulting free base of formula I can be transformed into a quaternary ammonium salt or an acid addition salt.

A compound of formula I in which R^2 or R^6 stands for an acyl radical can be prepared from a compound of formula I in which at least one of the radicals R^2, R^3 and R^6 represents a hydrogen atom by a treatment with an acyl halide or acyl anhydride in which the acyl radical is preferably an alkanoyl group having at most 6 carbon atoms; for example acetyl, or an aroyl group, for example benzoyl, in which the phenyl nucleus can be substituted as defined above, and the halogen may be chlorine. The reaction may be carried out in the presence of a base, for example an alkali metal carbonate, for example, potassium carbonate, or a tertiary amine, for example, triethylamine. The reaction can be accelerated by heating to the boiling point of the acylating agent. Again, a resulting salt may be converted into the free base or a resulting free base into a salt. Physiologically tolerable acid addition salts are, for example, formed with the following acids: hydrochloric acid, hydrobromic

acid and hydroiodic acid, phosphoric acid, sulphuric acid, methylsulphuric acid, amidosulphonic acid, nitric acid, tartaric acid, lactic acid, malonic acid, fumaric acid, oxalic acid, citric acid, malic acid, mucic acid, benzoic acid, salicylic acid, aceturic acid, embonic acid, naphthalene-1,5-disulphonic acid, ascorbic acid, phenylacetic acid, *p*-aminosalicylic acid, hydroxyethanesulphonic acid, benzenesulphonic acid, and synthetic resins containing acid groups, for example those having an ion exchange effect.

In both of the above procedures, if R^3 in the starting material is a hydrogen atom, this will be substituted, too, in the same way as R^2 or R^6.

The pyrimido(6,1-a)isoquinolin-2-one derivatives of the invention and their salts possess valuable pharmacological properties, for example blood pressure lowering properties as demonstrated in cats and dogs, bronchodilatory properties as demonstrated by antagonism to histamine-induced bronchoconstriction in guinea pigs and anti-allergic properties as demonstrated by the inhibition of passive cutaneous anaphylaxis (pca) in rats.

Because of their hypotensive activity, the compounds of the invention and their physiologically tolerable salts are suitable for the treatment and prevention of heart and circulatory diseases, for example essential and malignant hypertonia, heart insufficiency, Angina pectoris and disturbances of the peripheral circulation. The compounds and salts can be also be used in combination with other pharmacologically active substances, for example, diuretics, anti-arrhythmic agents, β-blockers, tranquilizers, heart vasodilating agents and hypolipidemics.

Because of their bronchodilatory and antiallergic effect, the compounds of the invention and their physiologically tolerable salts can be used for the treatment and prevention of diseases of the respiratory system, for example, bronchial asthma, chronic bronchitis, amphysema and allergies, for example, allergic asthma, hay fever, allergic rhinitis and conjunctivitis urticaria. The compounds and salts can also be used in combination with other pharmacologically active substances, for example, corticosteroids, sympathomimetics, xanthine derivatives, antihistamines, tranquilizers, and cardiac stimulants.

The compounds of the invention and their physiologically tolerable salts can be administered perorally, parenterally (intramuscularly, intravenously, subcutaneously) rectally, or topically, optionally in the form of an aerosol.

The following doses are used in mammals, particularly man: to reduce the blood pressure: a daily dose of 0.1 to 200 mg, dosage unit 0.1 to 25 mg; as bronchospasmolytic and antiallergic agent: a daily dose of 1 to 500 mg, dosage unit 1 to 100 mg.

The compounds of the invention and their physiologically tolerable salts can be administered either *per se* or in admixture or conjunction with a pharmaceutically suitable carrier material. For oral administration the active compounds may be admixed with the carrier and transformed into the usual form for administration, for example, tablets, push-fit capsules, aqueous alcoholic or oily suspensions or solutions. Suitable carrier materials are, for example, magnesium carbonate, milk sugar, maize starch, and magnesium stearate. The compositions can be prepared in the form of dry or moist granules. An oily carrier or solvents may be a vegetable or animal oil, for example sunflower oil or cod-liver oil.

In emergency situations, the active compounds may be administered intravenously. To this end, a compound of the invention or a physiologically tolerable salt thereof, as far as it has sufficient solubility, is generally dissolved in one of the usual auxiliaries, which may also act as a dissolving intermediary or buffer.

The solvents for intravenous administration are, for example, water, physiological sodium chloride solution and dilute alcohols, for example, ethanol, propanediol and glycerol; furthermore sugar solutions, for example, glucose and mannitol solutions, or a mixture of two or more of the aforesaid solvents.

The pharmaceutical preparations are preferably in unit dosage form, the preferred unit doses of the active substances being given above.

The following Examples illustrate the invention.

EXAMPLE 1

6,7-Dimethoxy-1-carbamoylmethylene-1,2,3,4-tetrahydroisoquinoline

Polyphosphoric acid (10.0 g) is heated to 100°C and 1.0 g of 6,7 - dimethoxy - 1 - cyanomethylene - 1,2,3,4 - tetrahydroisoquinoline is added under mechanical stirring. The reaction mixture is heated for 1 hour, poured into crushed ice and

made basic with 30% sodium hydroxide. The mixture is extracted with chloroform and the extract dried over anhydrous sodium sulphate. The solvent is evaporated under reduced pressure to give a white solid, yield 0.7 g, mp. 156—158°C.

EXAMPLE 2

9,10-Dimethoxy-3,4,6,7-tetrahydro-2*H* pyrimido(6,1-a)-isoquinolin-2,4-dione

A solution of 6,7 - dimethoxy - 1 - carbamoylmethylene - 1,2,3,4 - tetrahydroisoquinoline (5.0 g) and an excess of sodium ethoxide (prepared from 12.0 g of sodium metal and 600 ml of ethanol) in ethanol is heated. To the solution 150.0 ml of diethyl carbonate is added. The reaction mixture is refluxed for an additional 2.5 hr. The solvent is removed under vacuum and the residue is acidified to give a white precipitate, yield 4.80 g. The product crystallizes from dimethylformamide, mp. 323—325°C.

EXAMPLE 3

9,10-Dimethoxy-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido-(6,1-a)isoquinolin-2,4-dione

A mixture of 9,10 - dimethoxy - 3,4,6,7 - tetrahydro - 2*H* - pyrimido - (6,1-a)isoquinolin-2,4-dione (4.11 g), oilfree sodium hydride (0.75 g) and dimethylformamide (100 ml) is heated for 15 minutes to 100°C and then cooled to room temperature. Methyl iodide (10 ml) is added and the reaction mixture is heated for 12 hours to 100°C. The solvent is removed under reduced pressure and the residue treated with cold water. The solid matter is filtered off and recrystallized from ethyl acetate/methylene chloride. Yield 4.0 g, melting point 260—262°C.

EXAMPLE 4

9,10-Dimethoxy-3-isopropyl-3,4,6,7-tetrahydro-2*H*-pyrimido-(6,1-a)isoquinolin-2,4-dione

In a manner analogous to that of Example 3, 9,10 - dimethoxy - 3,4,6,7 - tetrahydro - 2*H* - pyrimido(6,1-a)isoquinolin - 2,4 - dione is reacted with isopropyl iodide. Yield 50%; melting point 190—192°C.

EXAMPLE 5

9,10-Dimethoxy-2-thio-2,3,6,7-tetrahydro-4*H*-pyrimido (6,1-a)isoquinolin-4-one

A mixture of 9,10 - dimethoxy - 3,4,6,7 - tetrahydro - 2*H* - pyrimido(6,1-a)isoquinolin - 2,4 - dione (10.0 g) and phosphorus pentasulfide (9.0 g) in 200 ml of pyridine is refluxed for 5 hours. Pyridine is removed under pressure. The residue is treated with dilute hydrochloric acid and then extracted with methylene chloride. The methylene chloride extract is dried over anhydrous sodium sulfate and evaporated to dryness leaving a white powder which is crystallized from chloroform-ether mixture, yield 10.0 g, m.p. 236—237°C.

EXAMPLE 6

9,10-Dimethoxy-3-methyl-2-thio-2,3,6,7-tetrahydro-4*H*-pyrimido(6,1-a)isoquinolin-4-one

Phosphours pentasulfide (1.0 g) is added to a solution of 9,10 - dimethyl - 3 - methyl - 3,4,6,7 - tetrahydro - 2*H* - pyrimido(6,1-a)isoquinolin - 2,4 - dione (0.5 g) in pyridine (10 ml). The mixture is refluxed for 15 hours, the solvent removed under reduced pressure and the residue repeatedly extracted with methylene chloride. The combined methylene chloride extracts are washed with dilute hydrochloric acid and with water, dried over sodium sulfate and evaporated to dryness. The residue is chromatographed to yield the desired compound. Yield 0.25 g, m.p. 230—231°C.

EXAMPLE 7

9,10-Dimethoxy-2-chloro-6,7-dihydro-4*H*-pyrimido (6,1-a)isoquinolin-4-one

A mixture of 30.0 g of 9,10 - dimethoxy - 3,4,6,7 - tetrahydro - 2*H* - pyrimido(6,1-a)isoquinolin - 2,4 - dione and 300 ml of phosphorus oxychloride is heated on a steam bath for 4 hours. The excess of phosphorus oxychloride is distilled under reduced pressure. The residue is poured into a cold solution of sodium hydroxide. A yellow solid precipitates which is collected by filtration. The product is purified by passage through a silica gel column using chloroform as eluent. Yield 28.0 g, m.p. 235—236°C.

EXAMPLE 8

9,10-Dimethoxy-2-butoxy-6,7-dihydro-4H-pyrimido (6,1-a)isoquinolin-4-one

To a mixture of sodium hydroxide (1.0 g) and n-butanol (50.0 ml) is added 9,10 - dimethoxy - 6,7 - dihydro - 2 - chloro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one (1.46 g). The reaction mixture is refluxed for 6 hours. The solvent is removed under reduced pressure. The residue is treated with water and extracted with chloroform. The extract is dried over anhydrous Na_2SO_4 and evaporated to give a white solid. After crystallization from chloroform-ether mixture, 0.7 g of the title compound is obtained, m.p. 158—159°C.

EXAMPLE 9

9,10-Dimethoxy-2-ethoxy-6,7-dihydro-4*H*-pyrimido (6,1-a)isoquinolin-4-one

A mixture of 3.0 g of 9,10 - dimethoxy - 3,4,6,7 - tetrahydro - 2*H* - pyrimido(6,1-a)isoquinolin - 2,4 - dione and 15.0 g of triethyloxonium fluoroborate in 100 ml of dichloromethane is stirred overnight. The reaction mixture is washed with a solution of sodium carbonate. The organic layer is separated and dried over anhydrous sodium sulfate. Evaporation of the solvent gives the title compound, yield 1.8 g.

EXAMPLE 10

9,10-Dimethoxy-2-methylmercapto-6,7-dihydro-4*H*-pyrimido (6,1-a)isoquinolin-4-one hydroiodide

To a suspension of 10.0 g of 9,10 - dimethoxy - 2 - thio - 2,3,6,7 - tetrahydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one in 200 ml of tetrahydrofuran, 20 ml of methyliodide is added and the reaction mixture refluxed for 4 hours. A white solid precipitates and is collected by filtration. It is crystallized from chloroform-methanol mixture, yield 10.50 g, m.p. 220—225°C (dec.)

EXAMPLE 11

General Procedure for the Preparation of Compounds of the General Formula I from Compounds of Formula III or IV

Compound III (X=S) or any one of the compounds IV (Y=Cl, SCH_3, OBu) is heated with an about equimolar amount of the appropriate amine of the general formula HNR_2R_3. The reaction is carried out in the presence of a base or an acid scavenger. The base is preferably the reacting amine itself, used in excess of that required for the reaction. The reaction is also preferably carried out in the presence of a suitable solvent as defined in the text. The reaction mixture may be heated to refluxing temperatures for 2—10 hours. The solvent is evaporated under reduced pressure. The residue is treated with water and extracted with an organic solvent. The extract is allowed to stand over anhydrous sodium sulfate and evaporated to dryness. The residue is purified by chromatography and/or crystallized to give the desired compound, which, if desired, is converted to its salt.

EXAMPLE 12

9,10-Dimethoxy-2-tert-butylamino-6,7-dihydro-4*H*-pyrimido (6,1-a)isoquinolin-4-one hydrochloride

A solution of 9,10 - dimethoxy - 2 - chloro - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one (3.0 g) and tert.-butylamine (10.0 ml) in chloroform (75 ml) is heated under reflux for 16 hours. The solvent is evaporated under reduced pressure and the residue triturated with a dilute solution of sodium hydroxide to give a white precipitate. The precipitate is filtered, dried and converted into its hydrochloride by treating it in solution in ethanol with hydrochloric acid. The hydrochloride is crystallized from ethanol-ether mixture, yield 3.0 g, m.p. 265—270°C.

EXAMPLE 13

9,10-Dimethoxy-2-sec-butylamino-6,7-dihydro-4*H*-pyrimido (6,1-a)isoquinolin-4-one hydrochloride

A solution of 9,10 - dimethoxy - 6,7 - dihydro - 2 - chloro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one (2.5 g) sec-butylamine (10 ml) and dimethylformamide (2 ml) is heated under reflux for 5 hours. The solvent and excess amine are distilled under reduced pressure. The residue is treated with

water. A white solid precipitates and is collected by filtration. The precipitate is crystallized from methylene chloride-ether mixture, yield 2.10 g. The crystals are dissolved in dichloromethane and treated with a solution of ethereal hydrochloric acid. The hydrochloride is crystallized from ethanol-ether mixture, m.p. 218—225°C.

EXAMPLE 14

9,10-Dimethoxy-2-(2,6-dimethylanilino)-6,7-dihydro-4*H*-pyrimido-(6,1-a)isoquinolin-4-one

A solution of 9,10 - dimethoxy - 2 - chloro - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one (2.5 g), 2,6-dimethylaniline (5.0 ml) in butanol (20.0 ml) is heated under reflux for 10 hours. The solvent is evaporated under reduced pressure to give a gummy mass. Chromatography of the gummy mass over silica gel using benzene-ethyl acetate as eluent gives the required product. The compound is crystallized from methanol, yield 2.0 g, m.p. 297—299°C.

EXAMPLE 15

9,10-Dimethoxy-2-(2,4-dimethylanilino)-6,7-dihydro-4*H*-pyrimido(6,1-a)isoquinolin-4-one

The procedure described in Example 14 is followed by using 2,4-dimethylaniline in place of 2,6-dimethylaniline. Yield: 75%, m.p. 239—241°C.

EXAMPLE 16

9,10-Dimethoxy-2-(2-chloroanilino)-6,7-dihydro-4*H*-pyrimido(6,1-a)isoquinolin-4-one hydrochloride monohydrate

The procedure described in Example 14 is followed, using 2-chloroaniline in place of 2,6-dimethylaniline. The hydrochloride is prepared as described in Example 12. Yield 70%, m.p. 182—186°C.

EXAMPLE 17

9,10-Dimethoxy-2-(2,4,6-trimethylanilino)-6,7-dihydro-4*H*-pyrimido(6,1-a)isoquinolin-4-one hydrochloride dihydrate

The procedure described in Example 14 is followed using 2,4,6-trimethylaniline in place of 2,6-dimethylaniline. The hydrochloride is prepared as described in Example 12. Yield 70%, m.p. 167—169°C.

EXAMPLE 18

9,10-Dimethoxy-3-methyl-2-mesitylimino-2,3,6,7-tetrahydro-4*H*-pyrimido(6,1-a)isoquinolin-4-one

A mixture of 9,10 - dimethoxy - 3 - methyl - 2 - thio - 2,3,6,7 - tetrahydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one (0.1 g) and methyl iodide (2 ml) in tetrahydrofurane (10 ml) is refluxed for 2 hours. The solid matter is filtered off and heated for 3 hours to 100 to 110°C together with 2,4,6-trimethylaniline (0.4 g). The excess trimethylaniline is removed by treating the reaction mixture with petroleum ether. The residue is worked up to give the desired compound, which is recrystallized from ethyl acetate/petroleum ether. Yield 80 mg, m.p. 151—152°C.

The same compound can also be obtained by direct reaction of 9,10 - dimethoxy - 3 - methyl - 2 - thio - 2,3,6,7 - tetrahydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one with 2,4,6-trimethylaniline.

EXAMPLE 19

9,10-Dimethoxy-3-methyl-2-n-butylimino-2,3,6,7-tetrahydro 4*H*-pyrimido(6,1-a)isoquinolin-4-one

In a manner analogous to that of Example 18 the compound is prepared from 9,10 - dimethoxy - 3 - methyl - 2 - thio - 3,4,6,7 - tetrahydro-4*H* - pyrimido(6,1-a)isoquinolin - 4 - one and n-butylamine. Yield 100%, m.p. 120—121°C.

EXAMPLE 20

General Procedure for the Preparation of Compounds of the Formula I from Compounds of Formulae Ia and Ib

The compound of formula Ia or Ib, in which R^3 preferably represents aryl is reacted, in the presence of a base, an acid scavenger, or a salt with a halide of the formula R^7X or R^8X. The halide can be used in equimolar amounts or in an excess.

The reaction is preferably carried out in the presence of a solvent as defined above. The reaction mixture may be refluxed for 2 to 50 hours. The solvent is evaporated under reduced pressure. The residue is treated with water and extracted with an organic solvent. The extract is dried over anhydrous sodium sulfate and the filtrate is evaporated to dryness. The residue is purified by chromatography and/or recrystallized to give the desired compound which can be transformed into its salt, if desired.

EXAMPLE 21

a) 9,10 - Dimethoxy - 3 - methyl - 2 - mesitylimino - 2,3,6,7 - tetrahydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one, its hydrochloride and methiodide and

b) 9,10 - Dimethoxy - 2 - (N - methyl - 2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one and its hydrochloride

A suspension of 9,10 - dimethoxy - 2 - (2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one (3.0 g), anhydrous potassium carbonate (15.0 g) and methyl iodide (45.0 ml) in acetone (300.0 ml) is heated under reflux for 15 hours. The reaction mixture is cooled and filtered. The filtrate is concentrated under reduced pressure whereby a residue is obtained. Chromatography of the residue over silica gel using benzene-chloroform (1:1) as eluent gives the desired free bases a) 2.3 g, m.p. 151—152°C and b) 0.15 g, m.p. 175—176°C. Further elution of the chromatography column with chloroform gives 0.35 g of the methiodide of base a) of m.p. 221—222°C. The hydrochlorides are prepared from the bases by the procedure described in Example 13. They are crystallized from dichloromethane/petroleum ether (b.p. 60—80°C) or dichloromethane/ethyl acetate or ethanol/diethyl ether. M.p. of hydrochloride a) 198°—200°C, m.p. of hydrochloride b) 189—191°C.

EXAMPLE 22

a) 9,10 - Dimethoxy - 2 - (N - isopropyl - 2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one and

b) 9,10 - dimethoxy - 3 - isopropyl - 2 - mesitylimino - 2,3,6,7 - tetrahydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one

9,10 - Dimethoxy - 2 - (2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one (5.85 g) and dimethylformamide (30 ml) are added to oil-free sodium hydride (1.5 g). The mixture is heated for 5 minutes to 110°C and then cooled to room temperature. Isopropyl iodide (2.55 g) is added and the whole is heated to 110°C for 40 hours. After cooling, methanol is added to the reaction mixture and the solvents are removed under reduced pressure. The residue is extracted with chloroform, the extract washed with water, dried over sodium sulfate and evaporated to dryness. The residue is chromatographed to give the bases a) m.p. 182—183°C and b) m.p. 178—179°C.

EXAMPLE 23

a) 9,10 - Dimethoxy - 2 - (N - ethyl - 2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one and

b) 9,10 - dimethoxy - 3 - ethyl - 2 - mesitylimino - 2,3,6,7 - tetrahydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one

Procedure A

Example 22 is repeated with the exception that ethyl iodide is used instead of methyl iodide.

Procedure B

9,10 - Dimethoxy - 2 - (2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one (0.5 g) and potassium fluoride (0.5 g) are added to dimethylformamide (10 ml). The mixture is heated to 100°C for 1 hour and then cooled. Ethyl iodide (0.2 g) is added and the whole is heated to 100°C for 40 hours. The solvent is removed under reduced pressure and the residue worked up as described in Example 22.

The procedures A and B yield the two isomers in different proportions. Free base a) m.p. 164—165°C; free base b) m.p. 142—143°C.

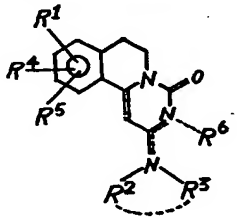
EXAMPLE 24

9,10-dimethoxy-2-(N-acetyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido-(6,1-a)isoquinolin-4-one

To an ice-cold solution of 9,10 - dimethoxy - 2 - (2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one (1.6 g) in chloroform (40.0 ml) is added first triethylamine (1.2 ml) and then dropwise a soluton of acetyl chloride (0.64 ml) in chloroform (10.0 ml). The mixture is stirred for 2 hours. The chloroform solution is washed successively with water, sodium carbonate solution and water, and is then dried over anhydrous sodium sulfate. The solution is filtered and the filtrate evaporated to dryness *in vacuo*. The residue is triturated with diethyl ether to yield the desired compound in solid form. Yield 1.6 g, m.p. 210—212°C (dichloromethane-petroleum ether b.p. 60—80°C).

WHAT WE CLAIM IS:—

1. Pyrimido(6,1-a)isoquinolin-4-one derivatives of the formula I



(I)

in which R^1, R^4 and R^5, which may be the same or different, each stands for a hydrogen atom, a hydroxy, alkoxy, dialkylphosphinylalkoxy, or acyloxy group, or a halogen atom, and two of the radicals R^1, R^4 and R^5 when in adjacent positions together may form a methylenedioxy or an ethylenedioxy group; R^2 and R^3, which may be the same or different, each stands for a hydrogen atom, a hydroxy, alkoxy, amino, alkylamino, dialkylamino, or arylamino group, or an amino or alkyl group substituted by a 5- or 6-membered carbon ring containing up to 3 hetero atoms, which may be the same or different, selected from nitrogen, oxygen and sulphur atoms, or an alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, halogenoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aralkyl, dialkylphosphinylalkyl, acyl or optionally substituted aryl group, aryl denoting an aromatic hydrocarbon radical having up to 10 carbon atoms, a heterocylic radical, or R^2 represents a pair of electrons if R^3 stands for one of the radicals defined below, or R^2 and R^3 when taken together with the nitrogen atom to which they are bound may form an optionally substituted nitrogen-containing heterocycle which may contain a further nitrogen or oxygen atom; and R^6 stands for a hydrogen atom or an alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, halogenoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aralkyl, heterocyclically substituted alkyl, dialkylphosphinylalkyl, acyl or optionally substituted aryl group, or R^6 represents a pair of electrons if R^2 represents one of the radicals defined above; and the acid addition salts and quaternary ammonium salts thereof.

2. A compound as claimed in claim 1, wherein a halogen atom represented by R^1, R^4 and/or R^5 is a chlorine atom and a dialkylphosphinylalkoxy radical is one in which the alkyl and alkoxy moieties contain at most 3 carbon atoms.

3. A compound as claimed in claim 1 or claim 2, wherein R^2, R^3 and/or R^6, as appropriate represents an alkylamino or dialkylamino radical in which the alkyl groups having at most 3 carbon atoms;

a phenylamino radical in which the phenyl residue is substituted one or more times, by the same or different substituents selected from halogen atoms, C_1—C_3 alkyl groups, and nitro groups;

an N-morpholinoamino radical;

an alkyl group having at most 6 carbon atoms, which may be substituted by one or two hydroxy or C_1—C_3 alkoxy groups, halogen atoms, amino or di(C_1—C_4 alkyl)amino groups;

a dialkylphosphinylalkyl group;

a cycloalkyl group having at most 6 carbon atoms;

an aralkyl group having at most 8 carbon atoms and which may be mono- or poly-substituted;

a furfuryl or tetrahydrofurfuryl radical;

a phenyl radical optionally substituted one or several times by the same or different substituents selected from halogen atoms C_1—C_3 alkyl and C_1—C_3 alkoxy groups, halogenoalkyl groups, amino, hydroxy and alkali metaloxy groups;

a pyrrolidino, piperidino, morpholino or piperazino radical which may be substituted by one or more substituents selected from alkyl, alkoxycarbonyl and aryl groups, and nitrogen-containing heterocycles; or

a linear or branched, C_1—C_6 alkanoyl group, or a benzoyl radical the phenyl residue of which may be substituted as defined above.

4. A compound as claimed in claim 1, wherein R^1 and R^4 each represents an alkoxy group;

R^5 represents a hydrogen atom;

R^2 represents a C_1—C_6 alkyl group or a phenyl group, optionally substituted as defined in claim 3; and

R^3 and R^6, which may be the same or different, each represents a hydrogen atom, a C_1—C_6 alkyl group, a cycloalkyl, substituted alkyl, aralkyl, heterocyclic alkyl, substituted aryl or C_1—C_6 alkanoyl group.

5. 9,10 - Dimethoxy - 2 - *tert.* - butylamino - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinoline - 4 - one hydrochloride.

6. 9,10 - Dimethoxy - 2 - (2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one hydrochloride dihydrate.

7. 9,10 - Dimethoxy - 3 - methyl - 2 - mesitylimino - 2,3,6,7 - tetrahydro - 2*H* - pyrimido(6,1-a)isoquinolin - 4 - one hydrochloride.

8. 9,10 - Dimethoxy - 2 - (N - methyl - 2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one hydrochloride.

9. 9,10 - Dimethoxy - 3 - isopropyl - 2 - mesitylimino - 2,3,6,7 - tetrahydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one hydrochloride.

10. 9,10 - Dimethoxy - 2 - (N - isopropyl - 2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one hydrochloride.

11. 9,10 - Dimethoxy - 3 - ethyl - 2 - mesitylimino - 2,3,6,7 - tetrahydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one hydrochloride.

12. 9,10 - Dimethoxy - 2 - (N - ethyl - 2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one hydrochloride.

13. 9,10 - Dimethoxy - 3 - acetyl - 2 - mesitylimino - 2,3,6,7 - tetrahydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one.

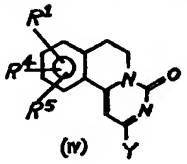
14. 9,10 - Dimethoxy - 2 - (N - acetyl - 2,4,6 - trimethylanilino) - 6,7 - dihydro - 4*H* - pyrimido(6,1-a)isoquinolin - 4 - one.

15. A compound as claimed in claim 1, substantially as described in Table 1 herein.

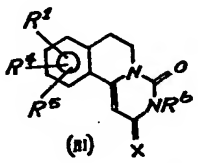
16. A compound as claimed in claim 1, substantially as described in any one of Examples 7 to 9, 13 to 16, and 20.

17. A process for the preparation of a compound as claimed in claim 1, wherein

(a) a compound of formula III or IV

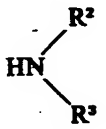


(IV)



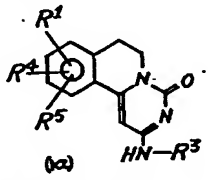
(III)

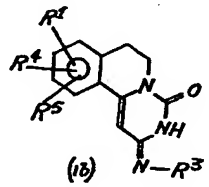
in which R^1, R^4, R^5 and R^6 are as defined in claim 1, X represents a sulphur atom and Y represents a halogen atom or an alkoxy or alkylthio group, is reacted with a compound of the formula



in which R^2 and R^3 are as defined in claim 1, with the proviso that they cannot represent acyl groups, and the resulting compound obtained is optionally acylated to give the corresponding compound of formula I in which R^2, R^3 or R^6 is acyl, or

(b) a compound of formula Ia or Ib


(Ia)


(Ib)

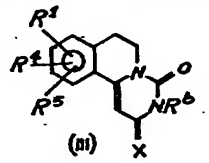
in which R^1, R^3, R^4 and R^5 are as defined in claim 1, is reacted with a compound of formula R^2X or R^6X, in which R^2 and R^6 each represents an alkyl, cycloalkyl, substituted alkyl, heterocyclic alkyl, aralkyl or an optionally substituted aryl group and X represents a halogen atom, or is reacted with an acyl halide or acyl anhydride, to give a compound of formula I in which R^2 and/or R^6 represents an acyl group and if R^3 in formula Ia or Ib represents a hydrogen atom, R^3 in formula I represents an acyl group.

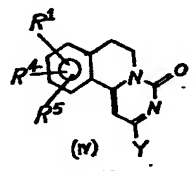
18. A process as claimed in claim 17, wherein a resulting free base is converted into an acid addition salt or a quaternary ammonium salt, or a resulting salt is converted into the free base or another salt.

19. A process as claimed in claim 17, carried out substantially as described in any one of Examples 7 to 9 and 11 to 24.

20. A compound as claimed in claim 1, whenever produced by a process as claimed in any one of claims 17 to 19.

21. A compound of the formula III or IV


(III)


(IV)

in which

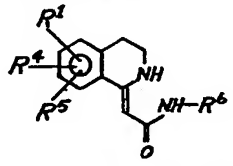
R^1, R^4, R^5 and R^6 are as defined in claim 1,

X represents an oxygen or sulphur atom and

Y represents a halogen atom or an alkoxy or alkylthio group, with the exception of the compound of formula III in which R^1, R^4, R^5 and R^6 are all hydrogen atoms and X is an oxygen atom.

22. A compound as claimed in claim 21, substantially as described in Table II herein.

23. A process for the preparation of a compound as claimed in claim 21, which comprises reacting a compound of the general formula V



in which R^1, R^4, R^5 and R^6 are as defined in claim 1 with a compound of the formula

$$R'-\underset{\underset{X}{\|}}{C}-R''$$

in which X is an oxygen atom and R' and R'' are both amino groups, halogen atoms or alkoxy groups, or R' represents an alkoxy group and R'' a halogen atom, and, if desired, carrying out any one or more of the following reactions, in any appropriate order:

(i) converting a compound of formula III in which X represents an oxygen atom into a compound of formula IV in which Y represents a halogen atom,

(ii) alkoxylating a compound of formula IV in which Y represents a halogen atom to obtain the corresponding compound in which Y represents an alkoxy group,

(iii) alkylating a compound of formula III in which X represents an oxygen atom to give a compound of formula IV in which Y represents an alkoxy group,

(iv) converting a compound of formula III in which X represents an oxygen atom into the corresponding compound in which X represents a sulphur atom,

(v) alkylating a compound of formula III in which X represents a sulphur atom to give a compound of formula IV in which Y represents an alkylthio group,

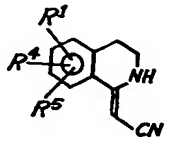
(vi) alkylating or acylating a compound of formula III in which X represents an oxygen atom and R^6 represents a hydrogen atom,

(vii) acylating a compound of formula III in which X represents a sulphur atom and R^6 represents a hydrogen atom.

24. A process as claimed in claim 23, carried out substantially as described in any one of Examples 2 to 6.

25. A compound as claimed in claim 21, whenever produced by a process as claimed in claim 23 or claim 24.

26. A process as claimed in claim 17, wherein a compound of formula III or IV has been produced by a process as claimed in claim 23 or claim 24, or a compound of formula V in which R^6 is a hydrogen atom, has been produced by treating a compound of formula VI



(VI)

in which R^1, R^4 and R^5 are as defined in claim 1, with an acid.

27. A compound as claimed in claim 1 or a salt thereof whenever produced by a process as claimed in claim 26.

28. A pharmaceutical preparation which comprises, as active substance, a compound or salt as claimed in any one of claims 1 to 16, claim 20 or claim 27, or a physiologically tolerable acid addition or quaternary ammonium salt thereof as appropriate, in admixture of conjunction with a pharmaceutically suitable carrier.

29. A pharmaceutical preparation as claimed in claim 28, in unit dosage form.

30. A pharmaceutical preparation as claimed in claim 29, for reducing the blood pressure, which comprises from 0.1 to 25 mg of the active substance per unit dose.

31. A pharmaceutical preparation as claimed in claim 29, for treating allergy and/or bronchiospasms, which comprises from 1 to 100 mg of the active substance per unit dose.

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